# General

## Guideline Title

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of tricyclic antidepressants: 2016 update.

## Bibliographic Source(s)

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, MÃ¼ller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017 Jul;102(1):37-44. [37 references]

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Hicks JK, Swen JJ, Thorn CF, Sangkuhl K, Kharasch ED, Ellingrod VL, Skaar TC, Muller DJ, Gaedigk A, Stingl JC. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013 May;93(5):402-8. [40 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

# NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

| Assessment | Standard of Trustworthiness |
|---|---|
| YES | Disclosure of Guideline Funding Source |
| | Disclosure and Management of Financial Conflict of Interests |

| | |
|---|---|
| | Guideline Development Group Composition |
| YES | Multidisciplinary Group |
| UNKNOWN | Methodologist Involvement |
| ▮▯▯▯▯ | Patient and Public Perspectives |
| | Use of a Systematic Review of Evidence |
| ▮▮▮▮▯ | Search Strategy |
| ▮▮▮▮▯ | Study Selection |
| ▮▮▮▯▯ | Synthesis of Evidence |
| | Evidence Foundations for and Rating Strength of Recommendations |
| ▮▮▮▮▯ | Grading the Quality or Strength of Evidence |
| ▮▮▮▮▮ | Benefits and Harms of Recommendations |
| ▮▮▮▮▯ | Evidence Summary Supporting Recommendations |
| ▮▮▮▮▮ | Rating the Strength of Recommendations |
| ▮▮▮▮▮ | Specific and Unambiguous Articulation of Recommendations |
| ▮▮▯▯▯ | External Review |
| ▮▮▮▮▯ | Updating |

# Recommendations

## Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Genetic Test Interpretation

Clinical laboratories usually interrogate for the more frequently observed cytochrome P450 2D6 (*CYP2D6*) and *CYP2C19* genetic variants and translate the results into star-allele (*) nomenclature. Each star-allele, or haplotype, is defined by a specific combination of single-nucleotide polymorphisms and/or other genetic variants within the gene locus of either *CYP2D6* or *CYP2C19*. Genetic test results are reported as the summary of inherited maternal and paternal star-alleles referred to as a diplotype (e.g., *CYP2D6*1/*2* and *CYP2C19*1/*1*). The alleles and their functional status can be found in the *CYP2D6* and *CYP2C19* Allele Definition Tables (see the "Availability of Companion Documents" field).

Scoring systems have been developed in an attempt to provide a uniform approach to quantitate the predicted functional status of *CYP2D6* alleles as follows: 1 for normal function, 0.5 for decreased function, and 0 for no function alleles (see Supplemental Material, *CYP2D6* Allele Definition Table [see the "Availability of Companion Documents" field]). The activity value for each allele of the diplotype is totaled

to provide a *CYP2D6* activity score. If *CYP2D6* gene duplications are detected, the activity value of the duplicated allele is multiplied by the number of duplications present before calculating the activity score (see Table 1 and Supplemental Tables S1 and S2 in the supplement). (See the Supplement for further explanation.)

Patients with two normal function *CYP2C19* alleles are categorized as normal metabolizers and individuals carrying one or two no function alleles are considered intermediate and poor metabolizers, respectively (see Table 1). Limited data suggest that *CYP2C19*17* may not compensate for no function alleles such as the *CYP2C19*2* allele. Therefore, patients carrying the *CYP2C19*17* increased function allele in combination with a no function allele are considered intermediate metabolizers. These phenotype assignments are analogous to those in the National Guideline Clearinghouse (NGC) summary of the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. (See the Supplement for discussion regarding CYP2C19 rapid metabolizer phenotype.)

Reference laboratories use varying methods to assign phenotypes. Before pharmacotherapy modifications are made based upon this guideline, it is advisable to determine a patient's phenotype as described above.

Table 1. Assignment of Likely Phenotypes Based on Diplotypes

| **Assignment of CYP2D6 Phenotype** | | | |
|---|---|---|---|
| **Likely Phenotype** | **Activity Score** | **Genotypes** | **Examples of Diplotypes** |
| Ultrarapid metabolizer (~1%-20% of patients)[a] | >2.0 | An individual carrying duplications of functional alleles | *(*1/*1)xN, (*1/*2)xN, (*2/*2)xN*[b] |
| Normal metabolizer (~72%-88% of patients) | 1.0-2.0[c] | An individual carrying two normal function alleles or two decreased function alleles or one normal and no function allele or one normal function and decreased function allele or combinations of duplicated alleles that result in an activity score of 1.0-2.0. | **1/*1, *1/*2, *2/*2, *1/*9, *1/*41, *41/*41, *1/*5, *1/*4* |
| Intermediate metabolizer (~1%-13% of patients) | 0.5 | An individual carrying one decreased function and one no function allele | **4/*41, *5/*9, *4/*10* |
| Poor metabolizer (~1%-10% of patients) | 0 | An individual carrying only no function alleles | **4/*4, (*4/*4)xN, *3/*4, *5/*5, *5/*6* |
| **Assignment of CYP2C19 Phenotype** | | | |
| **Likely Phenotype** | **Activity Score** | **Genotypes** | **Examples of Diplotypes** |
| Ultrarapid metabolizer (~2%-5% of patients)[a] | | An individual carrying two increased function alleles | **17/*17* |
| Rapid metabolizer (~2%-30% of patients) | | An individual carrying one normal function allele and one increased function allele | **1/*17* |
| Normal metabolizer (~35%-50% of patients) | | An individual carrying two normal function alleles | **1/*1* |

| Assignment of CYP2D6 Phenotype | | | |
|---|---|---|---|
| **Likely Phenotype** | **Activity Score** | **Genotypes** | **Examples of Diplotypes** |
| Intermediate metabolizer (~18%-45% of patients) | | An individual carrying one normal function allele and one no function allele or one no function allele and one increased function allele | *1/*2, *1/*3, *2/*17[d] |
| Poor metabolizer (~2%-15% of patients) | | An individual carrying two no function alleles | *2/*2, *2/*3, *3/*3 |

[a]CYP2D6 and CYP2C19 metabolizer status frequencies are based on average multiethnic frequencies. See the *CYP2C19* and *CYP2D6* Frequency Tables (see the "Availability of Companion Documents" field) for population-specific allele and phenotype frequencies.

[b]Where xN represents the number of *CYP2D6* gene copies.

[c]Patients with an activity score of 1.0 may be classified as intermediate metabolizers by some reference laboratories.

[d]The predicted metabolizer phenotype for the *CYP2C19 *2/*17* genotype is a provisional classification. The currently available evidence indicates that the *CYP2C19 *2/*17* increased function allele is unable to completely compensate for the *CYP2C19*2* no function allele.

See Supplemental Materials for a more comprehensive list of predicted metabolizer phenotypes.

Therapeutic Recommendations

CYP2D6 Dosing Recommendations

For neuropathic pain treatment, where lower initial doses of TCAs are used, gene-based dosing recommendations are found in the subsection "Gene-based dosing recommendations for neuropathic pain treatment" (below). Table 2, below, summarizes the gene-based dosing recommendations for *CYP2D6* and amitriptyline and nortriptyline for situations in which a higher initial dose is warranted, such as depression treatment. The recommended starting dose of amitriptyline or nortriptyline does not need adjustment for those with genotypes predictive of CYP2D6 normal metabolism. A 25% reduction of the recommended dose may be considered for CYP2D6 intermediate metabolizers. The strength of this recommendation is classified as moderate because patients with a CYP2D6 activity score of 1.0 are inconsistently categorized as intermediate or normal metabolizers in the literature, making these studies difficult to evaluate.

CYP2D6 ultrarapid metabolizers have a higher probability of failing amitriptyline or nortriptyline pharmacotherapy due to subtherapeutic plasma concentrations, and alternate agents are preferred. There are documented cases of CYP2D6 ultrarapid metabolizers receiving large doses of nortriptyline in order to achieve therapeutic concentrations. However, very high plasma concentrations of the nortriptyline hydroxy-metabolite were present, which may increase the risk for cardiotoxicity. If a tricyclic is warranted, there are insufficient data in the literature to calculate a starting dose for a patient with CYP2D6 ultrarapid metabolizer status, and therapeutic drug monitoring is strongly recommended. Adverse effects are more likely in CYP2D6 poor metabolizers due to elevated tricyclic plasma concentrations; therefore, alternate agents are preferred. If a tricyclic is warranted, consider a 50% reduction of the usual dose, and therapeutic drug monitoring is strongly recommended.

Table 2. Dosing Recommendations for Tricyclic Antidepressants Based on CYP2D6 Phenotype

| Phenotype | Implication | Therapeutic Recommendation[a,b] | Classification of Recommendation for Amitriptyline and Nortriptyline | Classification of Recommendation for Other TCAs[c] |
|---|---|---|---|---|
| CYP2D6 ultrarapid metabolizer | Increased metabolism of TCAs to less active compounds as compared with extensive metabolizers<br><br>Lower plasma | Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6.<br><br>If a TCA is warranted, consider titrating to a higher target dose | Strong | Optional |

| Phenotype | Implication | Therapeutic Recommendation[a,b] | Classification of Recommendation for Amitriptyline and Nortriptyline | Classification of Recommendation for Other TCAs[c] |
|---|---|---|---|---|
| | concentrations will increase probability of pharmacotherapy failure. | (compared to normal metabolizers).[d] Utilize therapeutic drug monitoring to guide dose adjustments. | | |
| CYP2D6 normal metabolizer | Normal metabolism of TCAs | Initiate therapy with recommended starting dose.[e] | Strong | Strong |
| CYP2D6 intermediate metabolizer | Reduced metabolism of TCAs to less active compounds compared to normal metabolizers<br><br>Higher plasma concentrations of active drug will increase the probability of side effects | Consider a 25% reduction of recommended starting dose.[e] Utilize therapeutic drug monitoring to guide dose adjustments.[d] | Moderate | Optional |
| CYP2D6 poor metabolizer | Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers<br><br>Higher plasma concentrations of active drug will increase the probability of side effects | Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6.<br><br>If a TCA is warranted, consider a 50% reduction of recommended starting dose.[e] Utilize therapeutic drug monitoring to guide dose adjustments.[d] | Strong | Optional |

[a]For tertiary amines (e.g., amitriptyline), if *CYP2C19* genotype results are also available, see Table 3, below, for *CYP2C19*-based dosing recommendations and Table 4, below, for *CYP2D6/CYP2C19*-based dosing recommendations.

[b]Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. See other considerations for dosing recommendations for conditions where lower initial doses are used, such as neuropathic pain.

[c]It may be reasonable to apply this recommendation to other TCAs also metabolized by CYP2D6 including clomipramine, desipramine, doxepin, imipramine, and trimipramine. There are fewer clinical and pharmacokinetic data supporting genotype-guided dose adjustments for these drugs when compared to amitriptyline or nortriptyline (see Supplemental Tables S8-S16).

[d]Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects.

[e]Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

CYP2C19 Dosing Recommendations

Dosing recommendations for neuropathic pain treatment with amitriptyline are found in the subsection "Gene-based Dosing Recommendations for Neuropathic Pain Treatment" below. Table 3, below, summarizes the gene-based dosing recommendations for CYP2C19 and amitriptyline when higher initial starting doses are warranted. The usual starting dose of amitriptyline may be used in CYP2C19 normal and intermediate metabolizers. Although CYP2C19 intermediate metabolizers would be expected to have a modest increase in the ratio of amitriptyline to nortriptyline plasma concentrations, the evidence does not indicate that CYP2C19 intermediate metabolizers should receive an alternate dose.

Patients taking amitriptyline who are CYP2C19 rapid or ultrarapid metabolizers may be at risk for having low plasma concentrations and an imbalance between parent drug and metabolites causing treatment failure and/or adverse events. Although the *CYP2C19*17* allele did not alter the sum of amitriptyline plus nortriptyline plasma concentrations, it was associated with higher nortriptyline plasma concentrations,

possibly increasing the risk of adverse events. For patients taking amitriptyline, extrapolated pharmacokinetic data suggest that CYP2C19 rapid or ultrarapid metabolizers may need a dose increase. Due to the need for further studies investigating the clinical importance of *CYP2C19*17* regarding tricyclic metabolism and the possibility of altered concentrations, CPIC recommends considering an alternative tricyclic or other drug not affected by CYP2C19. This recommendation is classified as optional due to limited available data. If amitriptyline is administered to a CYP2C19 rapid or ultrarapid metabolizer, therapeutic drug monitoring is recommended.

CYP2C19 poor metabolizers are expected to have a greater ratio of amitriptyline to nortriptyline plasma concentrations. The elevated amitriptyline plasma concentrations may increase the chance of a patient experiencing side effects. Consider a 50% reduction of the usual amitriptyline starting dose along with therapeutic drug monitoring.

Table 3. Dosing Recommendations of Tertiary Amines Amitriptyline, Clomipramine, Doxepin, Imipramine, and Trimipramine Based on CYP2C19 Phenotype

| Phenotype | Implication | Therapeutic Recommendation[a,b] | Classification of Recommendation for Amitriptyline | Classification of Recommendation for Other Tertiary Amine TCAs[c] |
|---|---|---|---|---|
| CYP2C19 ultrarapid metabolizer and CYP2C19 rapid metabolizer | Increased metabolism of tertiary amines compared to normal metabolizers<br><br>Greater conversion of tertiary amines to secondary amines may affect response or side effects | Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine<br><br>If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.[d] | Optional | Optional |
| CYP2C19 normal metabolizer | Normal metabolism of tertiary amines | Initiate therapy with recommended starting dose.[e] | Strong | Strong |
| CYP2C19 intermediate metabolizer | Reduced metabolism of tertiary amines compared to normal metabolizers | Initiate therapy with recommended starting dose.[e] | Strong | Optional |
| CYP2C19 poor metabolizer | Greatly reduced metabolism of tertiary amines compared to normal metabolizers<br><br>Decreased conversion of tertiary amines to secondary amines may | Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine<br><br>For tertiary amines, consider a 50% reduction of the recommended starting dose.[e] Utilize therapeutic drug monitoring to guide dose | Moderate | Optional |

| Phenotype | Implication | Therapeutic Recommendation[a,b] | Classification of Recommendation for Amitriptyline | Classification of Recommendation for Other Tertiary Amine TCAs[c] |
|---|---|---|---|---|
| | affect response or side effects | adjustments.[d] | | |

[a]If *CYP2D6* genotyping results are also available, see Table 2, above, for *CYP2D6*-based dosing recommendations and Table 3, above, for *CYP2D6/CYP2C19*-based dosing recommendations.

[b]Dosing recommendations apply only to higher initial doses of TCAs for treatment of conditions such as depression. See "Other Considerations," below, for dosing recommendations for conditions at which lower initial doses are used, such as neuropathic pain. For dosing guidelines for clomipramine, doxepin, imipramine, and trimipramine, see Supplementary Data.

[c]It may be reasonable to apply this recommendation to other TCAs also metabolized by CYP2C19 including clomipramine, doxepin, imipramine, and trimipramine. There are fewer clinical and pharmacokinetic data supporting genotype-guided dose adjustments for these drugs when compared to amitriptyline or nortriptyline (see Supplemental Tables S8-S16).

[d]Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects.

[e]Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

Other TCAs

Because the TCAs have comparable pharmacokinetic properties, it may be reasonable to extrapolate this guideline to other TCAs, including clomipramine, desipramine, doxepin, imipramine, and trimipramine (see Tables 2 and 3 above; see also Supplemental Tables S8-S16), with the acknowledgment that there are fewer data supporting dose adjustments for these drugs than for amitriptyline or nortriptyline.

CYP2D6 and CYP2C19 Combined Dosing Recommendations

Although specific combinations of *CYP2D6* and *CYP2C19* alleles are likely to result in additive effects on the pharmacokinetic properties of TCAs, little information is available on how to adjust initial doses based on combined genotype information. Patients carrying at least one *CYP2D6* no function allele and two *CYP2C19* normal function alleles had an increased risk of experiencing side effects when administered amitriptyline, whereas patients with at least one *CYP2C19* no function allele and two *CYP2D6* normal function alleles had a lower risk of experiencing side effects.

Combinatorial gene-based recommendations are provided in Table 4, below. Therapeutic drug monitoring may be advised if a tricyclic is prescribed to a patient with CYP2D6 ultrarapid, intermediate, or poor metabolism in combination with CYP2C19 ultrarapid, rapid, intermediate, or poor metabolism. There are sparse data in patients with a combinatorial CYP2C19 ultrarapid/rapid/intermediate/poor metabolizer phenotype and CYP2D6 ultrarapid/intermediate/poor phenotype. Because there are limited clinical or pharmacokinetic data regarding these combinatorial phenotypes, pharmacotherapy recommendations are classified as optional.

Table 4. Dosing Recommendations for Amitriptyline Based on Both CYP2D6 and CYP2C19 Phenotypes[a,b]

| Phenotype | CYP2D6 Ultrarapid Metabolizer | CYP2D6 Normal Metabolizer | CYP2D6 Intermediate Metabolizer | CYP2D6 Poor Metabolizer |
|---|---|---|---|---|
| CYP2C19 Ultrarapid or Rapid Metabolizer | Avoid amitriptyline use[c] Classification of recommendation[d]: Optional | Consider alternative drug not metabolized by CYP2C19[c,e] Classification of recommendation[d]: Optional | Consider alternative drug not metabolized by CYP2C19[c,e] Classification of recommendation[d]: Optional | Avoid amitriptyline use[c] Classification of recommendation[d]: Optional |
| CYP2C19 Normal Metabolizer | If amitriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers)[f,g] Classification of recommendation[d]: | Initiate therapy with recommended starting dose.[h] Classification of recommendation[d]: Strong | Consider a 25% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Moderate | Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] |

| Phenotype | CYP2D6 Ultrarapid Metabolizer | CYP2D6 Normal Metabolizer | CYP2D6 Intermediate Metabolizer | CYP2D6 Poor Metabolizer |
|---|---|---|---|---|
| | Strong | | Classification of recommendation[d]: Moderate | |
| CYP2C19 Intermediate Metabolizer | Avoid amitriptyline use[c] Classification of recommendation[d]: Optional | Initiate therapy with recommended starting dose.[h] Classification of recommendation[d]: Strong | Consider a 25% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Moderate | Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Moderate |
| CYP2C19 Poor Metabolizer | Avoid amitriptyline use[c] Classification of recommendation[d]: Optional | Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Moderate | Avoid amitriptyline use[c] Classification of recommendation[d]: Optional | Avoid amitriptyline use[c] Classification of recommendation[d]: Optional |

[a]Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. See "Other Considerations," below, for dosing recommendations for conditions where lower initial doses are used, such as neuropathic pain.

[b]The dosing recommendations are based on studies focusing on amitriptyline. Because tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply these guidelines to other tertiary amines including clomipramine, doxepin, imipramine, and trimipramine (the classification of this recommendation is optional).

[c]If amitriptyline is warranted, utilize therapeutic drug monitoring[f] to guide dose adjustment.

[d]See "CYP2D6 and CYP2C19 Combined Dosing Recommendations" above for explanation of classification of recommendations for this table.

[e]TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine.

[f]Utilizing therapeutic drug monitoring if a tricyclic is prescribed to a patient with CYP2D6 ultrarapid, intermediate, or poor metabolism in combination with CYP2C19 ultrarapid, intermediate, or poor metabolism is strongly recommended.

[g]Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects.

[h]Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

### Gene-based Dosing Recommendations for Neuropathic Pain Treatment

Amitriptyline is often used at lower dosages (e.g., 0.1 mg/kg/day in pediatric patients; initial doses of 25 mg daily may be prescribed to adults) for treatment of neuropathic pain compared to treatment for depressive disorders. Because of the lower dosage, it is less likely that CYP2D6 or CYP2C19 poor or intermediate metabolizers will experience adverse effects due to supratherapeutic plasma concentrations of amitriptyline. Therefore, the guideline authors recommend no dose modifications for poor or intermediate metabolizers when prescribed amitriptyline at a lower dose for treatment of neuropathic pain, but these patients should be monitored closely for side effects. If larger doses of amitriptyline are warranted, the guideline authors recommend following the gene-based dosing guidelines presented in Tables 2 to 4, above.

There are limited data to support dose recommendations for *CYP2C19*17* carriers who are prescribed amitriptyline at lower doses for neuropathic pain treatment. There are also few data describing the use of amitriptyline for neuropathic pain in CYP2D6 ultrarapid metabolizers. Based on predicted and observed pharmacokinetic data in those with depression, CYP2D6 ultrarapid metabolizers may be at an increased risk of failing amitriptyline therapy for neuropathic pain due to lower than expected drug concentrations, and thus alternative agents should be considered. Although there is sparse information on how to adjust

initial amitriptyline doses based on combined *CYP2D6* and *CYP2C19* genetic results when treating neuropathic pain, caution should be used when patients have a combination of poor or ultrarapid phenotypes (e.g., a CYP2D6 poor metabolizer also having CYP2C19 ultrarapid or poor metabolism).

Pediatrics

There are scarce studies focusing solely on *CYP2D6* or *CYP2C19* genotype and association with pharmacokinetic parameters or treatment outcomes of TCAs in pediatric patients. CYP2D6 activity is fully mature by early childhood, but CYP2C19 activity may be increased in children relative to adults. Although further genomic ontogeny studies are needed, there is a lack of evidence suggesting that this guideline cannot be extrapolated to pediatric patients.

Other Considerations

Consideration of Drug Interactions and Patient Characteristics

Patients treated for psychiatric disorders often require multiple medications, which can influence tricyclic plasma concentrations, side effects, and therapeutic failure. Recent data indicate that up to 20% of patients treated for depression may be converted to CYP2D6 poor metabolizer status. For example, patients taking amitriptyline in combination with a potent CYP2D6 inhibitor, such as fluoxetine, may have dramatic increases in amitriptyline plasma concentrations. It has been suggested that patients taking strong CYP2D6 inhibitors should be treated similarly to CYP2D6 poor metabolizers. Additionally, patients with increased age, liver disease, and reduced renal function may require reduced doses of TCAs. Drug–drug interactions along with patient characteristics should be considered in addition to the gene-based dosing recommendations presented herein.

Minor Metabolic Pathways of TCAs

Other cytochrome P450 enzymes, including CYP3A4 and CYP1A2, metabolize TCAs to a lesser extent. There is currently no strong evidence supporting gene-based dosing recommendations for other CYP enzymes that metabolize TCAs.

Definitions

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

- Psychiatric disorders, including depression and obsessive–compulsive disorder
- Pain, including neuropathic pain and migraine headache

## Guideline Category

Evaluation

Prevention

Risk Assessment

Treatment

## Clinical Specialty

Medical Genetics

Neurology

Pediatrics

Pharmacology

Psychiatry

Psychology

## Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

## Guideline Objective(s)

To provide information to allow the interpretation of existing cytochrome P450 2D6 (*CYP2D6*) and/or *CYP2C19* genotyping results to guide tricyclic antidepressant (TCA) dosing and selection

## Target Population

- Patients with psychiatric disorders or neuropathic pain
- Patients requiring migraine prophylaxis

## Interventions and Practices Considered

Use of cytochrome P450 2D6 (*CYP2D6*) and *CYP2C19* genotyping to guide therapeutic decision-making and dosing of tricyclic antidepressants (TCAs)

## Major Outcomes Considered

Effect of cytochrome P450 2D6 (*CYP2D6*) or *CYP2C19* on selective tricyclic antidepressants (TCAs) clinical outcomes or effect on TCA pharmacokinetic parameters

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

Retrieval of the Evidence Linking Genotype to Drug Variability

The PharmGKB Scientific Curator, the Clinical Pharmacogenetics Implementation Consortium (CPIC) coordinator or authors with experience in literature or systematic review conduct the literature review and present the results to the writing committee. A search of PubMed and OVID MEDLINE is performed using the keywords for the gene and drug of interest, for example: (gene name) OR (gene symbol) OR (dbSNP rs number) OR (gene common names) AND (drug name OR drug class name). Furthermore, papers listed on PharmGKB are cross-checked as there may be annotations for the papers and/or additional publications. Where available, evidence evaluating the outcomes when prescribing has been altered based on genetic testing is included. For most gene-drug pairs, randomized controlled trials comparing clinical outcomes with genotype-guided dosing versus conventional dosing are not available.

Literature Review

2012 Guideline

The authors searched the PubMed® database (1966 to September 2012) for the following keywords: (cytochrome P450 2D6 or CYP2D6) OR (cytochrome P450 2C19 or CYP2C19) AND (tricyclic antidepressants OR amitriptyline OR clomipramine OR desipramine OR doxepin OR imipramine OR nortriptyline OR trimipramine) for the association between *CYP2D6* and/or *CYP2C19* genotypes and metabolism of tricyclic antidepressant drugs or tricyclic antidepressant-related adverse drug events or clinical outcomes.

2016 Guideline Update

The authors searched PubMed® database as described above between September 2012 and July 2016. Using these search terms, 46 publications were identified.

The cytochrome P450 2D6 (*CYP2D6*) and *CYP2C19* Frequency Tables are updates of those previously published in CPIC guidelines. Updates to the *CYP2D6* and *CYP2C19* Frequency Tables were made by searching the PubMed® database (1995 to July 2016). The following criteria were used for *CYP2D6*: (CYP2D6 or 2D6 or cytochrome P4502D6) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve "full-text" and "English" literature. The following criteria were used for *CYP2C19*: (CYP2C19 or 2C19 or cytochrome P4502C19) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve "full-text" and "English" literature. In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion in the CYP2D6 or *CYP2C19* Frequency Table if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or genotype frequencies were reported, (3) the method by which the genes were genotyped was indicated, (4) the sample population consisted of at least 50 individuals with a few exceptions (e.g., smaller cohorts that were part of larger studies) and (5) the study represented an original publication (no reviews or meta-analyses).

*CYP2C19* diplotype and phenotype frequencies were estimated using the equation describing Hardy Weinberg equilibrium based on reported allele frequencies. *CYP2D6* allele frequency data have been

utilized by Gaedigk et al. to predict phenotype frequencies across world populations.

## Number of Source Documents

2012 Guideline

74 publications were reviewed and included in the evidence tables.

2016 Guideline Update

5 additional publications were reviewed and included in the evidence tables.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Levels of Evidence Linking Genotype to Phenotype

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* pharmacokinetic and pharmacodynamic data, *in vitro* enzyme activity of tissues expressing wild-type or variant-containing cytochrome P450 2D6 (*CYP2D6*) or *CYP2C19*, in vitro CYP2D6 or CYP2C19 enzyme activity from tissues isolated from individuals of known *CYP2D6* or *CYP2C19* genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

Summarization and Presentation of the Evidence Linking Genotype to Drug Variability

Publications supporting a major finding are usually considered as a group and scored by members of the writing committee based on the totality of the evidence supporting that major finding. Thus, it is possible for an evidentiary conclusion based on many papers, each of which may be relatively weak, to be graded as "moderate" or even "strong," if there are multiple small case reports or studies that are all supportive with no contradictory studies. The rating scheme (see the "Rating Scheme for the Strength of the Evidence" field) uses a scale modified slightly from Valdes et al. Primary publications are summarized in the Evidence Table which is published in the manuscript supplemental material (see the "Availability of Companion Documents" field). It is the writing committee's evaluation of this evidence that provides the basis for the therapeutic recommendation(s).

# Methods Used to Formulate the Recommendations

Expert Consensus

# Description of Methods Used to Formulate the Recommendations

Identification of Content Experts and Formation of Writing Committee

Once a guideline topic has been approved by Clinical Pharmacogenetics Implementation Consortium (CPIC) members and the Steering Committee, a senior author is identified through self-nomination or by request of the CPIC Steering Committee. The senior author takes responsibility for forming the writing committee and completing the guideline. The writing committee is multidisciplinary, comprising a variety of scientists, pharmacologists, and clinicians (e.g., pharmacists and physicians). Authors will have a track record of publication and/or expertise in the specific topic area of the guideline. PharmGKB assigns at least one Scientific Curator to each CPIC guideline writing committee who has expertise in searching, compiling and evaluating the evidence for gene-drug associations, and making it computable and available on the PharmGKB Web site. Furthermore, PharmGKB curators often take primary responsibility for completing background gene and drug summaries, assigning likely phenotypes based on genotypes (i.e., "Table 1" in guidelines), literature review, as well as preparing supplementary material provided in each guideline (i.e., genotypes that constitute the star (*) alleles or haplotypes, frequencies of alleles in major race/ethnic groups, genetic test interpretation and availability, and evidence linking genotype with phenotype).

Development of Therapeutic Recommendation and Assignment of Strength of the Recommendation

The writing committee discusses the evaluation of the literature and develops a draft recommendation via Web conferences and email communication. CPIC's therapeutic recommendations are based on weighing the evidence summarized in the supplementary Evidence Table from a combination of preclinical functional and clinical data, as well as on any existing consensus guidelines. Evidence related to the suitability of alternative medications or dosing that may be used based on genetics must be weighed in assigning the strength of the recommendation. Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians and are presented in the Table 2 of each guideline and occasionally in an algorithm.

To assign strength to a recommendation, CPIC uses a transparent three category system (see the "Rating Scheme for the Strength of the Recommendations" field) for rating recommendations that was adopted with slight modification from the rating scale for evidence-based recommendations on the use of antiretroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf ). Each recommendation also includes an assessment of its usefulness in pediatric patients.

CPIC guidelines currently focus on gene-drug pairs for which at least one of the prescribing recommendations is actionable (e.g., recommendation to alter a dose or consider an alternative drug based on the genotype-phenotype relationship). For these and many other gene-drug pairs, PharmGKB also contains clinical annotations that are genotype-based summaries of the association between a drug and a particular variant. Each clinical annotation is assigned a level of evidence depending on population, replication, effect size and statistical significance.

Refer to "Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process" (see the "Availability of Companion Documents" field) for additional information.

# Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

## Cost Analysis

Genotyping cost-effectiveness is beyond the scope of this guideline.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

Internal and External Review, Comment, and Approval Process

Once the writing committee has completed and approved a draft guideline, the draft guideline is circulated to the Clinical Pharmacogenetics Implementation Consortium (CPIC) co-leaders and coordinator for content review. The guideline is reviewed for compliance with the CPIC Standard Operating Procedures and required format. The guideline draft is then discussed on a CPIC conference call with all CPIC members and circulated to the members for further review and approval. At each stage, feedback is considered for incorporation into the guideline and/or revision of the guideline, as supported by the available evidence and expert clinical judgment of the senior author and writing committee. Finally, the guideline manuscript under goes typical external scientific peer review by the journal prior to publication. Current agreements with the American Society for Clinical Pharmacology and Therapeutics give the journal *Clinical Pharmacology and Therapeutics* the first right of refusal for publication of CPIC guidelines; as part of this agreement, the guidelines are freely posted to PharmGKB immediately upon publication. In general *Clinical Pharmacology and Therapeutics* uses a minimum of two external expert peer-reviewers and an editorial board member with content expertise as reviewers for each CPIC guideline.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The evidence summarized in Supplemental Tables S5-S16 (see the "Availability of Companion Documents" field) is graded using a scale based on previously published criteria that was applied to other Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines. Every effort was made to present evidence from high-quality original research studies. In addition, the authors took into consideration all available peer-reviewed published literature including other gene-based dosing recommendations.

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

For patients who have existing cytochrome P450 2D6 (*CYP2D6*) and/or *CYP2C19* genotyping test results, the potential benefit is identifying those patients who are at an elevated risk of experiencing side effects or therapeutic failure. For those patients, dose adjustments can be made or an alternative agent selected.

## Potential Harms

- A limitation inherent to most commercially available genotyping tests is that rare or *de novo* variants are not detected. Additionally, some alleles are not well characterized, resulting in uncertainty when predicting the phenotype for some genetic test results. Genotyping is reliable when performed in qualified reference laboratories, but, as with any laboratory test, an error can occur. Any errors in genotyping or phenotype prediction, along with the presence of a rare genomic variant not tested for, could potentially have lifelong implications for the patients' drug therapy.
- Patients may be predisposed to treatment failure or adverse effects due to genetic variation in cytochrome P450 2D6 (*CYP2D6*) altering drug clearance or in *CYP2C19* altering the ratio of parent drug to metabolites. Common adverse effects include anticholinergic, central nervous system, and cardiac effects. Tertiary and secondary amines along with their metabolites each have unique side effect profiles, as detailed in Supplemental Table S4 (see the "Availability of Companion Documents" field).

# Qualifying Statements

## Qualifying Statements

Tricyclic antidepressant (TCA) plasma concentrations have been shown to be predictive of toxicity and efficacy, with guidelines defining therapeutic ranges for TCAs. However, there are less data supporting a direct correlation between genotype and response when compared to the correlation between genotype and plasma concentrations. Some studies describe a relationship between genotype and response, while other studies do not. Therefore, this guideline takes into consideration both clinical outcomes and observed tricyclic plasma concentrations based on genotype/phenotype characteristics.

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

The application of genotype-based dosing is most appropriate when initiating therapy with a tricyclic. Obtaining a pharmacogenetic test after months of drug therapy may be less helpful in some instances, given that the drug dose may have already been adjusted based on plasma concentrations, response, or side effects. Similar to all diagnostic tests, genetic tests are one of several pieces of clinical information that should be considered before initiating drug therapy.

Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for a patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to persons or property arising out of or

related to any use of CPIC's guidelines, or for any errors or omissions.

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Underlying Assumption

The key underlying assumption for all CPIC guidelines is that clinical high-throughput and pre-emptive genotyping will eventually become common practice and clinicians will increasingly have patients' genotypes available before a prescription is written. Therefore, CPIC guidelines are designed to provide guidance to clinicians as to how available genetic test results should be interpreted to ultimately improve drug therapy, rather than to provide guidance as to whether a genetic test should or should not be ordered.

# Implementation of the Guideline

## Description of Implementation Strategy

Implementation of This Guideline

The guideline supplement contains resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see "Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support section" of the Supplement [see the "Availability of Companion Documents" field]).

Refer to "Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process" (see the "Availability of Companion Documents" field) for information on guideline dissemination and connecting the guidelines to practice.

## Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Getting Better

Living with Illness

Staying Healthy

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, MÃ¼ller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017 Jul;102(1):37-44. [37 references]

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2017 Jul

## Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

## Source(s) of Funding

This work was funded by the National Institutes of Health (NIH) for Clinical Pharmacogenetics Implementation Consortium (CPIC) (R24GM115264) and PharmGKB (R24GM61374).

## Guideline Committee

The Writing Committee

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

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Conflict of Interest

A.G. is a paid consultant of Millennium Laboratories. T.E.K is a paid scientific advisor to the Rxight Pharmacogenetic Program. K.S. has received research support from Shionogi & Co., Ltd., Eli Lilly Japan, K.K., Yoshitomi Pharmaceutical Industries, Ltd., Meiji Seika Pharma Co., Ltd., Eisai Co., Ltd., Pfizer Inc., GlaxoSmithKline K.K., Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo Co., and Takeda Pharmaceutical Co., Ltd., and honoraria from Kowa Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Meiji Seika Pharma Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Ono Pharmaceutical Co., Ltd., GlaxoSmithKline K.K., and Eisai Co., Ltd. All other authors declare no conflict of interest.

Management of Conflicts of Interest

All authors must declare any funding interests and activities potentially resulting in conflict of interest by written disclosure to the Clinical Pharmacogenetics Implementation Consortium (CPIC) Steering Committee and writing committee before the approval of the authorship plan. Included are all possible conflicts including spouses/family members in declarations, National Institutes of Health (NIH) funding that could be interpreted to indicate that authors are "advocates" of the recommendations, as well as any sources of revenue from consulting, patents, stock ownership, etc. All conflicts of interest are reported in the guideline manuscript.

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Hicks JK, Swen JJ, Thorn CF, Sangkuhl K, Kharasch ED, Ellingrod VL, Skaar TC, Muller DJ, Gaedigk A, Stingl JC. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013 May;93(5):402-8. [40 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from the Clinical Pharmacogenetics Implementation Consortium (CPIC) Web site .

## Availability of Companion Documents

The following are available:

Supplementary material, including tables and methodological information, is available from the

Clinical Pharmacogenetics Implementation Consortium (CPIC) Web site.
A variety of resources, including definition, frequency, functionality, and diplotype-phenotype tables; drug mapping; gene resource mapping; and clinical decision support, are available from the CPIC Web site.
Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. 2014;15(2):209-17. Available from the CPIC Web site.

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on May 15, 2013. The information was verified by the guideline developer on June 25, 2013. This summary was updated by ECRI Institute on September 14, 2017. The updated information was verified by the guideline developer on October 30, 2017.

This NEATS assessment was completed by ECRI Institute on August 31, 2017. The information was verified by the guideline developer on October 30, 2017.

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